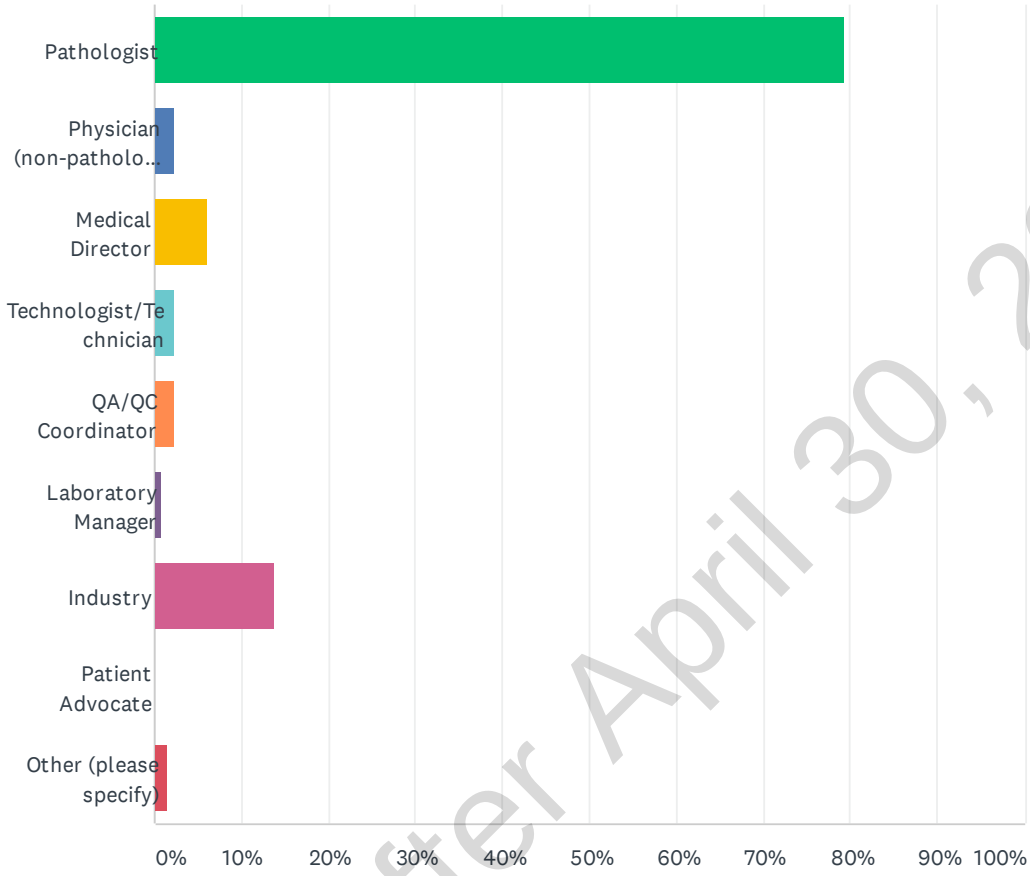
# Q1 What is your occupation/role? (select all that apply)

Answered: 130 Skipped: 0

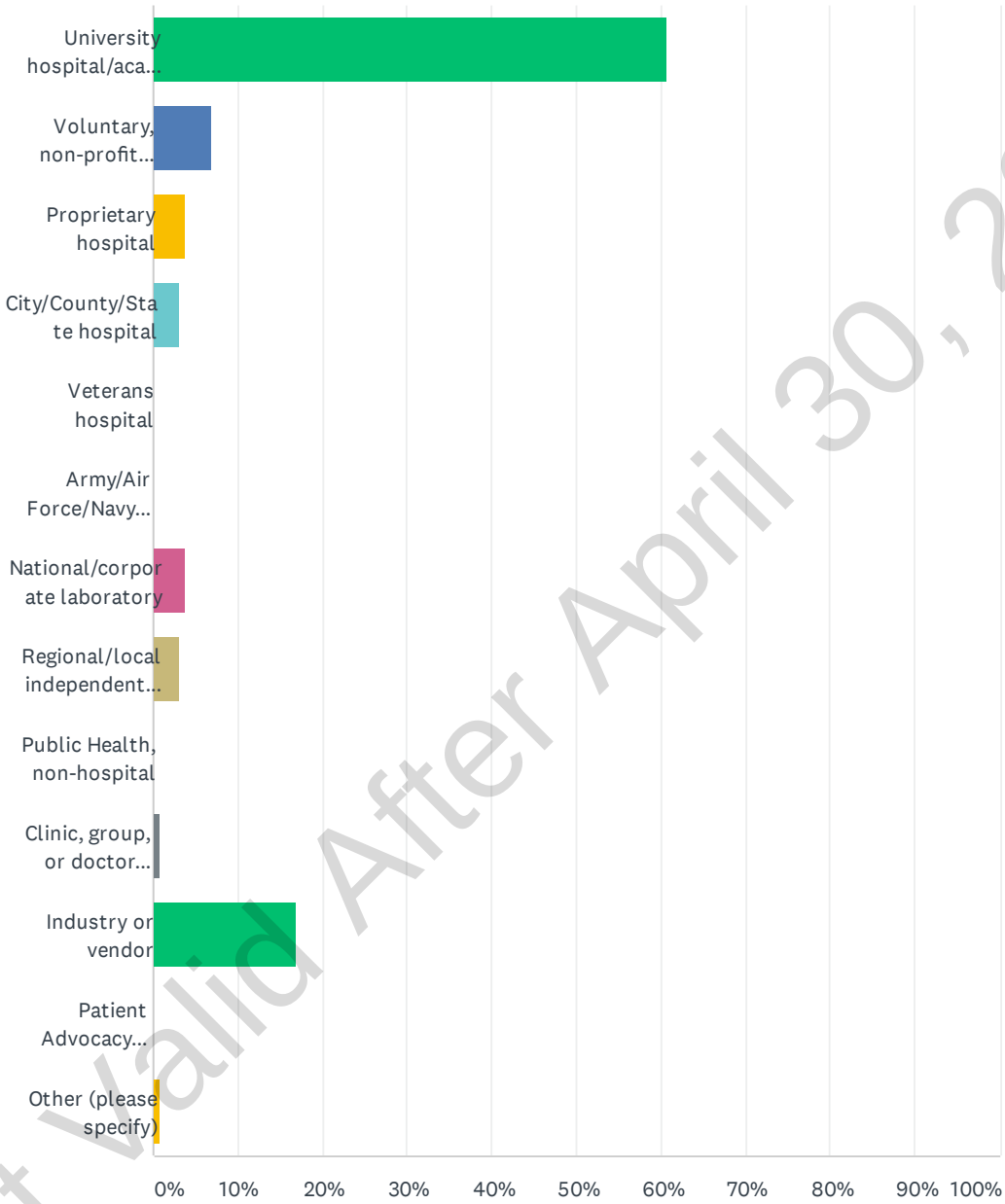



| ANSWER CHOICES | RESPONSES | |
|---|---|---|
| Pathologist | 79.23% | 103 |
| Physician (non-pathologist) | 2.31% | 3 |
| Medical Director | 6.15% | 8 |
| Technologist/Technician | 2.31% | 3 |
| QA/QC Coordinator | 2.31% | 3 |
| Laboratory Manager | 0.77% | 1 |
| Industry | 13.85% | 18 |
| Patient Advocate | 0.00% | 0 |
| Other (please specify) | 1.54% | 2 |
| Total Respondents: 130 | | |

| # | OTHER (PLEASE SPECIFY) | DATE |
|---|---|---|
| 1 | na | 4/5/2021 11:58 AM |
| 2 | cytopathologist | 4/3/2021 4:36 AM |

# Q2 Which of the following best describes your practice setting? (select one)

Answered: 130 Skipped: 0

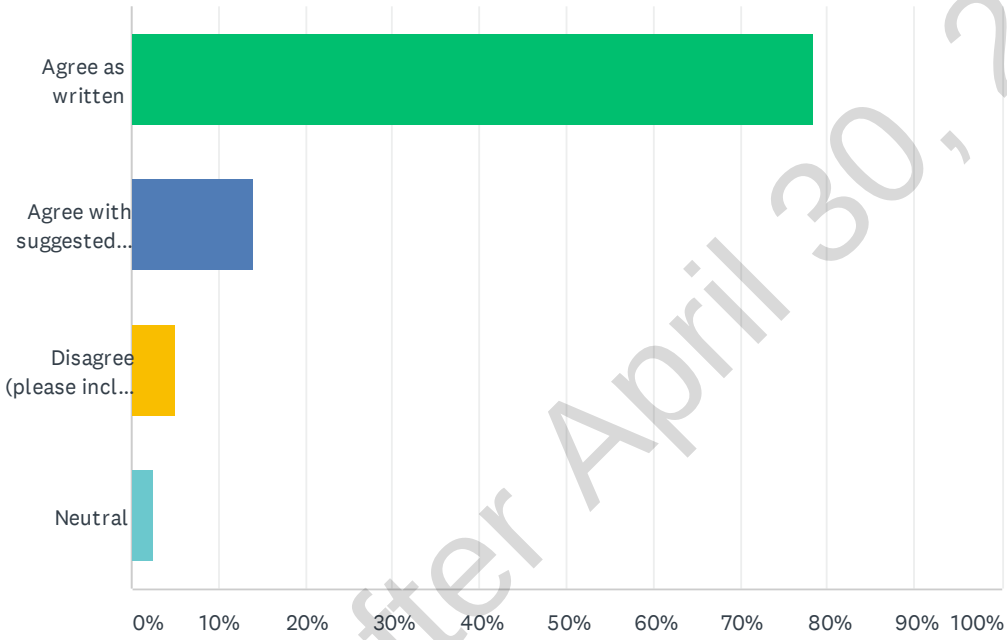


| ANSWER CHOICES | RESPONSES | |
|---|---|---|
| University hospital/academic medical center | 60.77% | 79 |
| Voluntary, non-profit hospital | 6.92% | 9 |
| Proprietary hospital | 3.85% | 5 |
| City/County/State hospital | 3.08% | 4 |
| Veterans hospital | 0.00% | 0 |
| Army/Air Force/Navy hospital | 0.00% | 0 |
| National/corporate laboratory | 3.85% | 5 |
| Regional/local independent laboratory (except clinic or group practice and not owned by a national corporation(s)) | 3.08% | 4 |
| Public Health, non-hospital | 0.00% | 0 |
| Clinic, group, or doctor office laboratory | 0.77% | 1 |
| Industry or vendor | 16.92% | 22 |
| Patient Advocacy Organization | 0.00% | 0 |
| Other (please specify) | 0.77% | 1 |
| TOTAL | | 130 |

| # | OTHER (PLEASE SPECIFY) | DATE |
|---|---|---|
| 1 | na | 4/5/2021 11:58 AM |

# Q3 Draft Recommendation Statement 1In patients with advanced non-small cell lung cancer (NSCLC), clinicians should use a validated PD-L1 immunohistochemical (IHC) expression assay, in conjunction with other targetable genomic biomarker assays where appropriate, to optimize selection for treatment with immune checkpoint inhibitors. (Certainty of Evidence: Moderate; Strength of Recommendation: Strong)

Answered: 79 Skipped: 51




| ANSWER CHOICES | RESPONSES | |
|---|---|---|
| Agree as written | 78.48% | 62 |
| Agree with suggested modifications (please include comments) | 13.92% | 11 |
| Disagree (please include comments) | 5.06% | 4 |
| Neutral | 2.53% | 2 |
| TOTAL | | 79 |

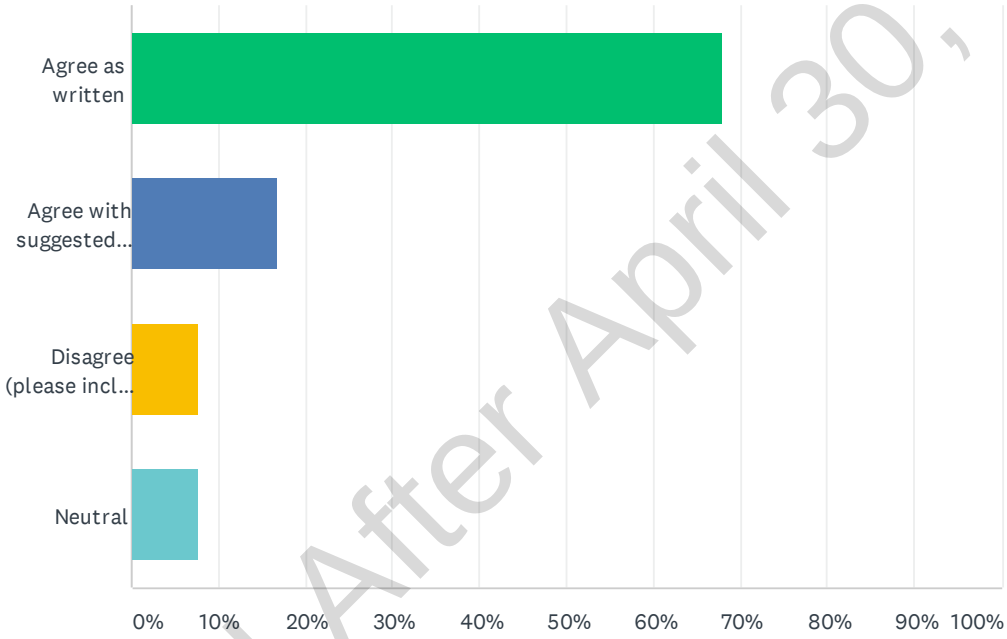
| # | COMMENTS | DATE |
|---|---|---|
| 1 | Comment for Statement 2 PDL1 should be tested on a good quality tumor tissue sample. A biopsy is fine and it doesn't need to be repeated on a better resection specimen. | 4/29/2021 12:10 PM |
| 2 | strike out advanced | 4/28/2021 9:59 AM |
| 3 | The wording on "targetable genomic biomarker assays" is very vague, it just create more questions. There should be more specific indication, based on trials data, on what "genomic biomarkers" would discourage the use of IO therapy, e.g. EGFR and ALK+ patients. | 4/28/2021 8:48 AM |
| 4 | instead of validated PDL1 assay, specify companion diagnostics. replace clinicians with pathologists | 4/28/2021 2:14 AM |
| 5 | I think mutational burden testing (and potentially other assays still in development) has huge | 4/26/2021 10:00 AM |

| | | |
|---|---|---|
| | advantages over IHC. The wording here discourages these other assays, and will tend to lock practices in place. FOR DRAFT 2: I would explicitly state that Cytology samples can be an optimal specimen for testing. Clinicians have the impression that cytology is Sub-optimal for testing. | |
| 6 | Please consider the role of PD-L1 testing in the evolving treatment landscape of early NSCLC. Please refer to the following press release for further detail (https://www.gene.com/media/press-releases/14901/2021-03-21/pivotal-phase-iii-study-shows-genentechs). Data will be submitted to health authorities globally and presented at an upcoming medical meeting. Suggest to remove the word "advanced" NSCLC. Suggest to emphasize that testing should be performed irrespective of histological subtype in particular as targetable genomic biomarker assays may only be used in non-squamous patients in clinical practice. | 4/22/2021 10:04 PM |
| 7 | • Rather than validated PD-L1 IHC expression assay, suggest saying an FDA-approved PD-L1 companion diagnostic and/or clinically validated PD-L1 IHC assay  Rationale is the approved companion diagnostics are what were used in the clinical trials to identify patients who will respond to the immune checkpoint inhibitor • “in conjunction with other targetable genomic biomarker assays where appropriate”  This is not totally clear, suggest further clarifying • TMB high is not a first line indication for NSCLC • TMB is not a targetable genomic biomarker (targetable genomic biomarkers include KRAS, EGFR, ROS1, etc.) define targetable genomic biomarkers • PD-L1 and targeted genomic biomarkers are mutually exclusive For Statement 2 below: • Overall agree, but cytology samples may not be appropriate specimen to test. If appropriate, suggest calling that out | 4/22/2021 6:14 AM |
| 8 | “In patients with advanced non-small cell lung cancer (NSCLC), clinicians should use a validated PD-L1 immunohistochemical (IHC) expression assay, in conjunction with other targetable genomic biomarkers, as recommended in current professional guidelines, to optimize selection for treatment with immune checkpoint inhibitors.” Notes to reviewers/Rationale: To avoid tissue depletion with iterative testing, consider incorporating language inclusive of broad molecular testing using a comprehensive genomic profiling assay. EGFR and ALK are examples of targetable genomic biomarkers that should be considered for testing. Package inserts for checkpoint inhibitors state that NSCLC patients whose tumors are positive for EGFR and/or ALK genomic tumor aberrations should not be considered for first-line checkpoint inhibitor therapy, even if they are PD-L1 positive. References: KEYTRUDA (pembrolizumab) package insert: https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf TECENTRIQ (atezolizumab) package insert: https://www.gene.com/download/pdf/tecentriq_prescribing.pdf YERVOY (ipilimumab) package insert: https://packageinserts.bms.com/pi/pi_yervoy.pdf | 4/21/2021 3:24 PM |
| 9 | Strike the word 'advanced' Clinicians should use a 'clinically' or 'FDA-approved' validated PD-L1 IHC expression assay | 4/20/2021 5:32 PM |
| 10 | Please write "CD274 (PD-L1)". If that's not possible, please write "PD-L1 (CD274)" as a second choice. Please see an opinion paper by The Gene Product Nomenclature Consortium (GPNC), Fujiyoshi K et al. PNAS 2021 on this very issue at https://www.pnas.org/content/118/3/e2025207118 | 4/15/2021 1:06 PM |
| 11 | Validated PD-L1 IHC with definite scoring criteria should be used | 4/8/2021 3:32 PM |
| 12 | Strike out "advanced" | 4/7/2021 3:43 PM |
| 13 | PD-L1 may give too simplistic view into IO-response predictions although it seems to be the most important IO-response predictor also on the mRNA-level. See e.g. https://www.synapse.org/#!Synapse:syn24180900/wiki/608579 | 4/6/2021 6:11 AM |
| 14 | Since PD-L1 testing is usually performed in pathology lab, I would suggest to modify statement "...clinicians should use..." The preffered PD-L1 testing method should be PD-L1 IHC assay. | 4/6/2021 1:51 AM |
| 15 | Vague recommendation. Should lab use FDA approved test? If not validated by whom and how? Why is recommendation strong based on moderate evidence? | 4/1/2021 6:56 PM |
| 16 | I recommend changing "optimize" to "facilitate" | 4/1/2021 11:02 AM |
| 17 | I would clarify the validation point to specify whether we mean an FDA approved companion diagnostic test with its validated antibody clone. From talking with clinicians about PD-L1 testing recommendations and interpretation, it is clear that many are confused about the | 3/31/2021 4:36 PM |

| | | |
|---|---|---|
| | distinction between companion diagnostics and research-use only tests, the difference between CPS and TPS, and using a companion diagnostic off-label to prescribe a different drug. | |

# Q4 Draft Recommendation Statement 2Clinicians should test for PD-L1 expression using the best available specimen. Note: Laboratories should ensure appropriate validation has been performed on all specimen types and fixatives. Specific validation requirements are out of scope with this guideline and laboratories should refer to the CAP's "Principles of Analytic Validation of Immunohistochemical Assays" guideline for details on how to validate IHC specimens.(Certainty of Evidence: Low; Strength of Recommendation: Conditional)

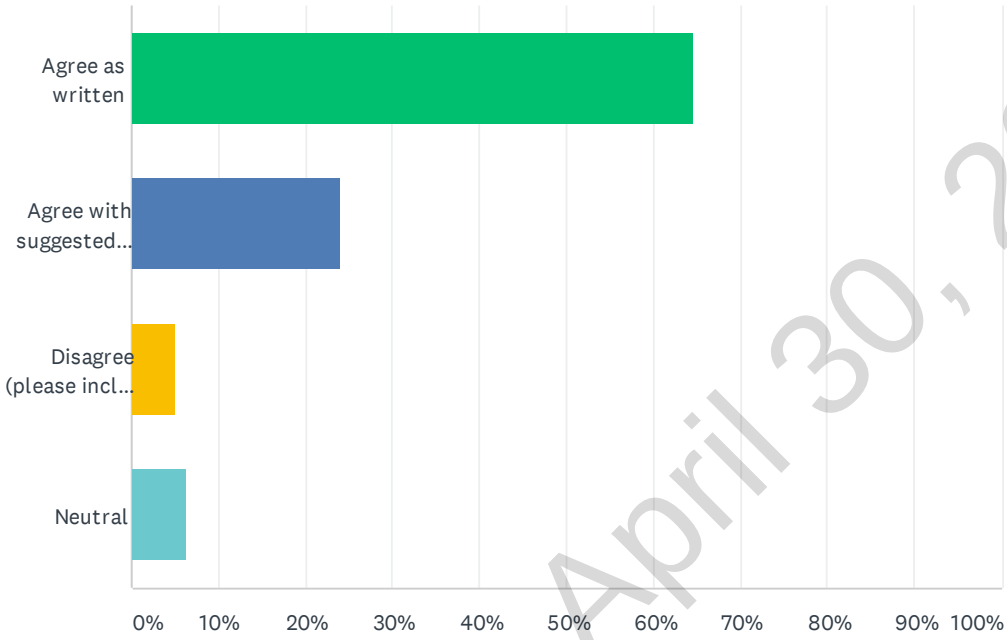
Answered: 78 Skipped: 52




| ANSWER CHOICES | RESPONSES | |
|---|---|---|
| Agree as written | 67.95% | 53 |
| Agree with suggested modifications (please include comments) | 16.67% | 13 |
| Disagree (please include comments) | 7.69% | 6 |
| Neutral | 7.69% | 6 |
| TOTAL | | 78 |

# Q5 Draft Recommendation Statement 3When feasible, laboratorians should use clinically validated PD-L1 IHC assays as intended. (Certainty of Evidence: Low; Strength of Recommendation: Conditional)

Answered: 79 Skipped: 51




| ANSWER CHOICES | RESPONSES | |
|---|---|---|
| Agree as written | 64.56% | 51 |
| Agree with suggested modifications (please include comments) | 24.05% | 19 |
| Disagree (please include comments) | 5.06% | 4 |
| Neutral | 6.33% | 5 |
| TOTAL | | 79 |

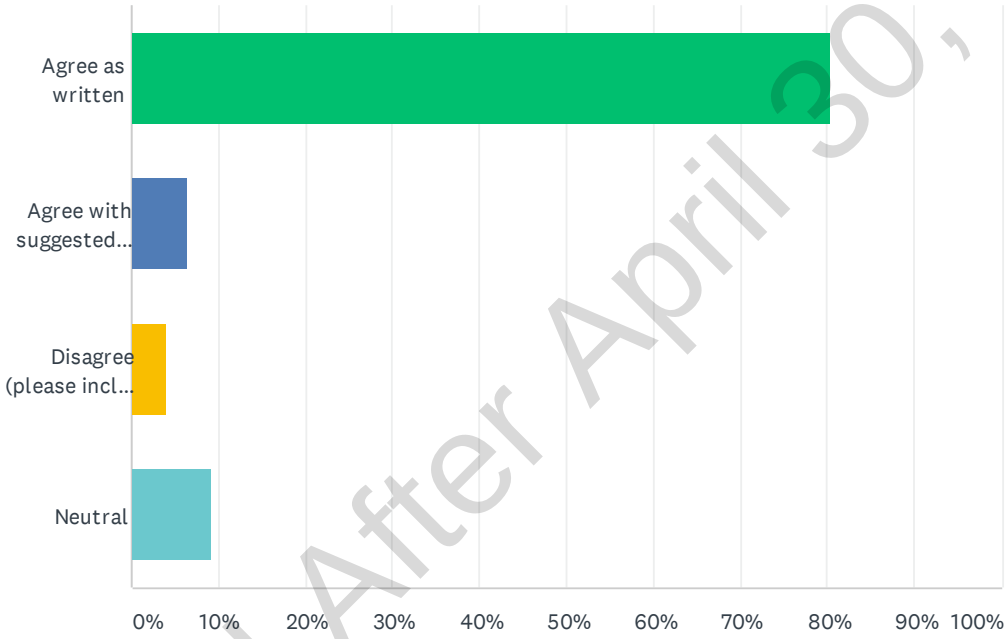
| # | COMMENTS | DATE |
|---|---|---|
| 1 | The phrase "best available specimen" is very general. How is this defined and what factors should be considered in the determination of the "best" status? | 4/30/2021 3:18 PM |
| 2 | omit "clinically" | 4/29/2021 12:10 PM |
| 3 | The antibody is probably important but I am not sure the immunostainer used is - if it is validated and shows same results as the recommended. | 4/29/2021 8:51 AM |
| 4 | please clarify: as intended | 4/28/2021 9:59 AM |
| 5 | The certainty of evidence should be at least be moderate, not low. For draft recommendation statement 2, the word "best available specimen" is very vague and capture only half the pathology aspect of the recommendation. It should also include consideration from clinical side, e.g. growing tumor, accessibility, etc. | 4/28/2021 8:48 AM |
| 6 | what is the 'best available specimen'? Please specify - does it mean the specimen where the score is highest, or the specimen that is most cellular? Instead of clinically validated - companion diagnostics | 4/28/2021 2:14 AM |

| | | |
|---|---|---|
| 7 | Laboratorians should use clinically validated PD-L1 IHC Assays as validated. | 4/26/2021 2:03 PM |
| 8 | This does not seem to say anything useful. Are you trying to say that Pathologists should not use experience and good judgement to tinker with assays that have been clinically validated? There can be good reasons for adjusting assays, and improvements in our field of pathology could be inhibited by this language. | 4/26/2021 10:00 AM |
| 9 | this box popped up after filling in 'disagree'with statement 2; see comment 4 | 4/26/2021 5:43 AM |
| 10 | We suggest the inclusion of a statement acknowledging the importance of efforts to improve communication between oncologists, proceduralists and pathologists/cytologists which should be recognized as essential to molecular and diagnostic biomarker testing. Consistent, open communication is key to ensure: • that teams establish a consistent and reliable plan for adequate tissue acquisition during the procedure to reduce QNS rates. If not already done, a direct reference should be made to existing sample adequacy guidelines recently published by CAP. • appropriate handling of specimens, including limitation of IHC stains to preserve tissue for molecular and diagnostic biomarker testing. • utilization and triage of all cytologic specimens for PD-L1 testing, including pleural fluid. • recognition of evidence based efforts to improve communication channels, including implementation at some cancer centers of an established biomarker testing tumor board to ensure that discussions regarding the importance of biomarker testing are conducted between multidisciplinary specialists. | 4/23/2021 10:19 AM |
| 11 | Comment box for Statement 2 appears to be missing: Suggest to refer clinicians to the assay's package insert for appropriate specimen types, fixatives, fixative durations, slide age, etc. Agree as written with draft recommendation 3. | 4/22/2021 10:04 PM |
| 12 | • Suggest clarifying: “When feasible, laboratorians should use the FDA-approved companion diagnostic or clinically validated PD-L1 IHC assays that is paired with the associated therapeutic as intended” • When not feasible or in the alternative, laboratories should use a rigorously validated LDT | 4/22/2021 6:14 AM |
| 13 | Intended by whom? | 4/21/2021 10:16 AM |
| 14 | Remove 'When feasible' Add 'laboratorians and 'clinicians' 'as intended' needs to be clarified | 4/20/2021 5:32 PM |
| 15 | Value of using clinically validated assays as intended stands in their clinical utility. If there is enough evidence to support this statement then this should be shown in the recommendation | 4/20/2021 5:38 AM |
| 16 | Rather than "when feasible", I suggest using " laboratarians are recommended to use clinically validated.. " | 4/17/2021 4:25 PM |
| 17 | Please write "CD274 (PD-L1)". If that's not possible, please write "PD-L1 (CD274)" as a second choice. Please see an opinion paper by The Gene Product Nomenclature Consortium (GPNC), Fujiyoshi K et al. PNAS 2021 on this very issue at https://www.pnas.org/content/118/3/e2025207118 | 4/15/2021 1:06 PM |
| 18 | The validated PDL-1 assay with continual EQA participation should be adequate. | 4/13/2021 2:08 AM |
| 19 | Laboratorians and clinicians | 4/7/2021 2:20 PM |
| 20 | Validated assays may fail. Use of suitable control tissues on each slide & Participation into regular quality rounds is a must. See e.g. https://www.nordiqc.org/epitope.php?id=107 | 4/6/2021 6:11 AM |
| 21 | Or laboratory developed test with certified external quality assurance | 4/6/2021 2:08 AM |
| 22 | Instead of "clinicians" more appropriate term is "pathologists". Specify "best available specimen" - does it relate to primary or secondary tumor. What is the difference between statemet 1 and 3 in regards to PD-L1 assay (validated PD-L1 IHC expression assay vs clinically validated PD-L1 IHC assay). | 4/6/2021 1:51 AM |
| 23 | I agree that it should be clinically validated, however this goes back to ensuring the optimal set up clinical trials etc. The PD L1 story is really how not to proceed, as when licensed originally it could only be done on one platform which many hospitals did not now currently have and also did not consider how practise regarding EBUS cytology had progressed - therefore logistically caused many issues until the larger studies then showed how the antibodies and platforms equilibrated and how cytology specimens could be included. So as to avoid this in future there needs to clear cognisance given to all of these issues and this will then ensure that labs will only use those markers truly clinically validated for such studies. | 4/4/2021 6:39 AM |
| 24 | For rec's 2 and 3 and 4, be sure that final documents reference the updated CAP validations | 4/3/2021 12:35 PM |

| | | |
|---|---|---|
| | guidelines (in process), not the 1st edition. Also, should be clear that FDA approved/cleared assays need to be verified before implementing--this will be covered in IHC validation guidelines as well. | |
| 25 | Statement 2 needs to be fleshed out. Is it the most recent specimen? The specimen that has more tumor? Why list evidence as low, this is almost self evident so nobody is going to do studies to create evidence Statement 3 needs to be fleshed out, it is in contradiction with statement 1. Why is it needed altogether? | 4/1/2021 6:56 PM |
| 26 | This statement is rather open ended. Elaborate on "as intended". As intended per package insert, as used in the clinical trial or what exactly? | 4/1/2021 1:49 PM |
| 27 | Approved platform not widely available. Evidence most clones perform similarly. | 4/1/2021 1:41 PM |
| 28 | I would clarify the validation point to specify whether we mean an FDA approved companion diagnostic test with its validated antibody clone. From talking with clinicians about PD-L1 testing recommendations and interpretation, it is clear that many are confused about the distinction between companion diagnostics and research-use only tests, the difference between CPS and TPS, and using a companion diagnostic off-label to prescribe a different drug. | 3/31/2021 4:36 PM |

# Q6 Draft Recommendation Statement 4Laboratories that choose to use laboratory developed tests (LDTs) for PD-L1 expression should validate according to the requirements of their accrediting body.Note: Specific validation requirements are out of scope with this guideline and laboratories should refer to the CAP's "Principles of Analytic Validation of Immunohistochemical Assays" guideline for details on how to validate IHC specimens.(Certainty of Evidence: Low; Strength of Recommendation: Strong)

Answered: 76 Skipped: 54



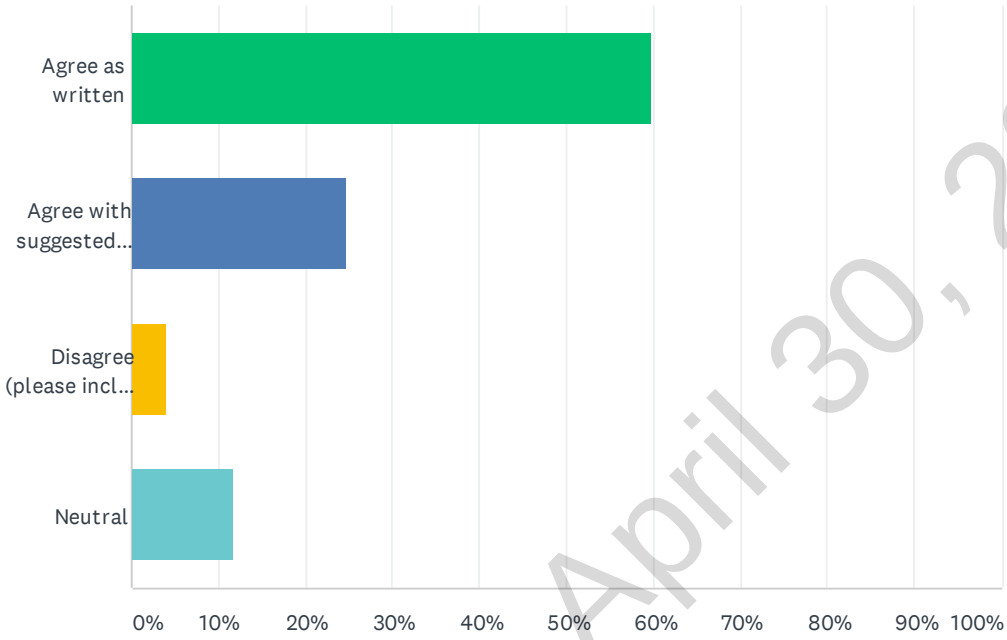

| ANSWER CHOICES | RESPONSES | |
|---|---|---|
| Agree as written | 80.26% | 61 |
| Agree with suggested modifications (please include comments) | 6.58% | 5 |
| Disagree (please include comments) | 3.95% | 3 |
| Neutral | 9.21% | 7 |
| TOTAL | | 76 |

| # | COMMENTS | DATE |
|---|---|---|
| 1 | should this be encouraged? | 4/28/2021 2:14 AM |
| 2 | Statement 4 (and 2): Strong Recommendations: Laboratories that choose to use laboratory developed tests (LDTs) for PD-L1 expression should validate according to the requirement of their accrediting body. Note: Specific validation requirements are out of scope with this guideline and laboratories should refer to the CAP's IHC Validation Guideline for details on how to validate IHC specimens. Although the panel did not consider this her task, they make a statement for following CAP's IHC Validation Guideline for details on how to validate IHC | 4/26/2021 5:43 AM |

| | | |
|---|---|---|
| | specimens. However, there is also knowledge published on indirect clinical validation of the Pd-L1 IHC assay in comparison with a clinically validated assay. The reference[1] shown below plus the responses by others provide to my opinion a better approximation than the CAP guidelines for proper threshold setting of a predictive LDT. Erik Thunnissen References [1] Thunnissen E. How to Validate Predictive Immunohistochemistry Testing in Pathology? A Practical Approach Exploiting the Heterogeneity of Programmed Death Ligand-1 Present in Non–Small Cell Lung Cancer. Arch Pathol Lab Med 2019;143:11–2. https://doi.org/10.5858/arpa.2018-0410-ED. | |
| 3 | Using LDT's is suboptimal in this setting. Should use approved assay, or send out if not feasible. | 4/21/2021 10:16 AM |
| 4 | Clinical evidence is not feasible with an LDT such as drug trial evidence and outcomes | 4/20/2021 5:32 PM |
| 5 | Please write "CD274 (PD-L1)". If that's not possible, please write "PD-L1 (CD274)" as a second choice. Please see an opinion paper by The Gene Product Nomenclature Consortium (GPNC), Fujiyoshi K et al. PNAS 2021 on this very issue at https://www.pnas.org/content/118/3/e2025207118 | 4/15/2021 1:06 PM |
| 6 | LDTs may work well too. See e.g.https://www.nordiqc.org/epitope.php?id=107 | 4/6/2021 6:11 AM |
| 7 | Lab should participate with PD-L1 test in EQA. | 4/6/2021 1:51 AM |
| 8 | For rec's 2 and 3 and 4, be sure that final documents reference the updated CAP validations guidelines (in process), not the 1st edition. | 4/3/2021 12:35 PM |
| 9 | It is questionable to refer to the IHC principle because the paper was released before the development of PD-L1 assays. So, the note should be dropped. | 4/2/2021 1:05 AM |
| 10 | It doesn't make sense to issue strong recommendations based on low evidence. | 4/1/2021 6:56 PM |

# Q7 Draft Recommendation Statement 5Laboratorians should report PD-L1 immunohistochemistry results using a percent expression score.(Certainty of Evidence: Very Low; Strength of Recommendation: Conditional)

Answered: 77 Skipped: 53



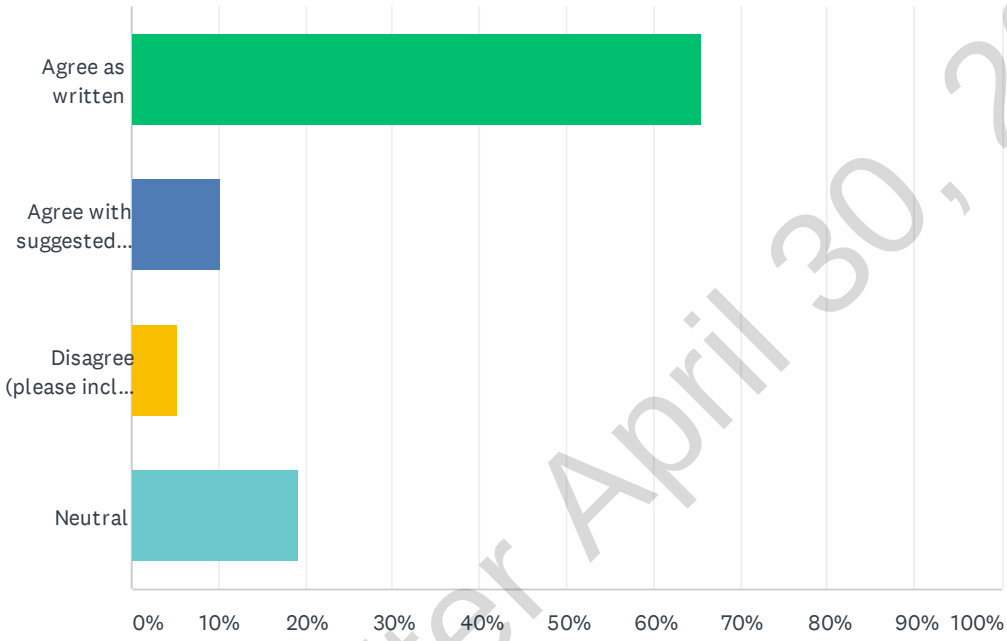

| ANSWER CHOICES | RESPONSES | |
|---|---|---|
| Agree as written | 59.74% | 46 |
| Agree with suggested modifications (please include comments) | 24.68% | 19 |
| Disagree (please include comments) | 3.90% | 3 |
| Neutral | 11.69% | 9 |
| TOTAL | | 77 |

| # | COMMENTS | DATE |
|---|---|---|
| 1 | This may be somewhat tumor type and context dependent. Seems like there could also be a role for a qualitative assessment based upon the approved PD-L1 cut-off for IO treatment for the tumor type in question. Reproducibility of low PD-L1 percentile estimates is often limited, therefore, providing a single percentile score without qualification may impart a false impression of accuracy. | 4/30/2021 3:18 PM |
| 2 | We use a percentage score but I think a graded scoring would be more reproducible | 4/29/2021 8:51 AM |
| 3 | please specify percent expression score in which cell type(s), according also to type of antibody and rules | 4/28/2021 9:59 AM |
| 4 | suggest slight modification on the wording: Laboratories should include in report of PD-L1 immunohistochemistry results the percent expression score. | 4/28/2021 8:48 AM |
| 5 | suggest adding "using the percentage cut-offs provided by the specific assay" | 4/28/2021 2:14 AM |
| 6 | Option of reporting based in clinical cutoffs only, ie <1%, 1-49% and 50% or higher. | 4/26/2021 10:34 AM |

| | | |
|---|---|---|
| 7 | Suggest to include a reference that assay-specific scoring criteria described in package inserts should be reported in addition to a percent expression score, as applicable | 4/22/2021 10:04 PM |
| 8 | • Suggest clarifying that the score format should match the PD-L1 assay used, for example 22C3 TPS %, SP142 TC % | 4/22/2021 6:14 AM |
| 9 | Add the word 'tumor' before 'expression score'. | 4/20/2021 5:32 PM |
| 10 | Please write "CD274 (PD-L1)". If that's not possible, please write "PD-L1 (CD274)" as a second choice. Please see an opinion paper by The Gene Product Nomenclature Consortium (GPNC), Fujiyoshi K et al. PNAS 2021 on this very issue at https://www.pnas.org/content/118/3/e2025207118 | 4/15/2021 1:06 PM |
| 11 | It seems like the scoring depends on the specific PDL1 antibody used. I would consider rephrasing to state the scoring should be c/w the PDL1 antibody and intended usage. | 4/15/2021 9:30 AM |
| 12 | This recommendation did not explicitly state whether tumor proportion score (TPS) or combined proportion score (CPS) should be used. If there is room, it may be worth adding a qualifier to the current recommendation statement such as "... using a percent expression score of tumor and/or immune cells when applicable". | 4/10/2021 10:13 AM |
| 13 | Should use the scoring system recommended for tumor type, preferred companion diagnostic, and antibody clone i.e. TPS or CPS | 4/8/2021 11:11 PM |
| 14 | TPS is not precisely a %, it should state "a percent of expression or score | 4/7/2021 2:20 PM |
| 15 | 0 - 100% is recommendable. Bins 1-5% should be avoided! | 4/6/2021 6:11 AM |
| 16 | TPS in 5 -10% range according to known cut-offs for treatment | 4/6/2021 2:08 AM |
| 17 | in brackets (TPS - tumor proportion score). | 4/6/2021 1:51 AM |
| 18 | I am neutral here, as really I feel that the most important issue is ensuring that the cut-offs for treatment algorithms are achieved as correctly as possible. | 4/4/2021 6:39 AM |
| 19 | A bit difficult...although most ICIs for NSCLC use a PD-L1 IHC assay with a TPS readout, what about if/when an assay might rely on a combined CPS? I agree that an actual percent score (and not a range/bucket) reporting should be provided, if that is the intention of this recommendation. Would likely be clarified in the text following this recommendation. | 4/3/2021 4:26 PM |
| 20 | Is this % tumor cell expression (TPS)? Specify explicitly? | 4/3/2021 12:35 PM |
| 21 | SP142 uses a different scoring system, so "... using the scoring system of the corresponding clinical trials" may be better. | 4/2/2021 1:05 AM |
| 22 | This is a standard way of expressing IHC. Statement could be explained not to use +,++ or +/-. Again it is silly to quote this as very low evidence and conditional. Authors may benefit from reading article on Evidence Based Medicine mocking the lack of evidence for the utility of parachutes | 4/1/2021 6:56 PM |
| 23 | Should we report results based on cut off like > or = 1 or > or = 50% rather than exact % as it can be very subjective?What difference does it make between 20% and 30%? | 4/1/2021 2:08 PM |
| 24 | The scoring system selected needs to be concordant with the intended use of the assay and may, depending on tissue type, may not be a percentage, but rather a categorical or calculated score, | 3/31/2021 9:08 PM |
| 25 | Laboratorians should report PD-L1 immunohistochemistry results using a percent expression score, according to either the scoring guidelines published by the manufacturer, or as recommended by the US FDA. | 3/31/2021 7:41 PM |
| 26 | very low certainty of evidence + conditional strength = consider moving this to good practice statement instead. This recommendation feels more like "gut feeling" or "wishful thinking" rather than evidence based. However, I do not have the evidence in front of me that framed this recommendation. | 3/31/2021 4:08 PM |
| 27 | Verbiage needs modification. | 3/31/2021 2:15 PM |

# Q8 Draft Recommendation Statement 6Clinicians should not use tumor mutation burden alone to select patients with advanced NSCLC for immune checkpoint inhibitors based on insufficient evidence in this population.(Certainty of Evidence: Low; Strength of Recommendation: Conditional)

Answered: 78 Skipped: 52



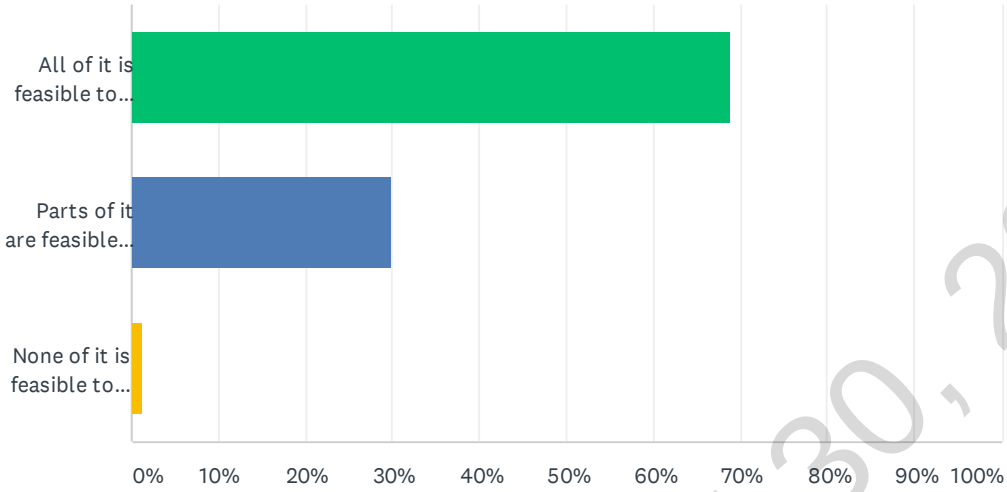

| ANSWER CHOICES | RESPONSES | |
|---|---|---|
| Agree as written | 65.38% | 51 |
| Agree with suggested modifications (please include comments) | 10.26% | 8 |
| Disagree (please include comments) | 5.13% | 4 |
| Neutral | 19.23% | 15 |
| TOTAL | | 78 |

| # | COMMENTS | DATE |
|---|---|---|
| 1 | suggest modifying the wording | 4/28/2021 2:14 AM |
| 2 | I can imagine scenarios in which clinicians would be unable to treat a patient based on an available TMB result together with their clinical judgement unless the patient gets another biopsy for IHC. You could get a good clinician in trouble with this language if there were an adverse event. It is also likely that better assays than IHC should emerge, and this language will tend to hinder innovation. Much of medicine is based on judgement: if all areas of medicine in which judgement were required were simply not allowed to happen (as this wording suggests), there is no question patients would suffer and medicine would stagnate. | 4/26/2021 10:00 AM |
| 3 | We suggest that Statement 6 be worded similarly to the other statements. For example, “Tumor mutation burden alone does not have sufficient validity to select patients with advanced NSCLC who are first line candidates for immunotherapy.” | 4/23/2021 10:19 AM |

| | | |
|---|---|---|
| 4 | We would like to ask the committee to consider an alternative wording: There is currently insufficient prospective evidence that TMB can be used independently to select for advanced NSCLC patients who would benefit from immune checkpoint inhibitor mono-therapy. | 4/22/2021 10:04 PM |
| 5 | • Suggest revising for clarity – Clinicians should use tumor mutation burden to select patients with advanced NSCLC for immune checkpoint inhibitors only when no satisfactory alternative treatment option is available / add comment to indicate aligning to an approved PI • TMB is not approved to select patients for ICI therapy as a first line treatment | 4/22/2021 6:14 AM |
| 6 | Revised Recommendation Statement 6: “Clinicians should consider tumor mutational burden (TMB) evaluation in NSCLC patients who are PD-L1 negative and have progressed following prior treatment, and who have no satisfactory alternative treatment options to checkpoint inhibitor therapy.” Notes to reviewers/Rationale: Testing for TMB status may offer therapeutic options where otherwise there were none, either because tumors were test-negative for PD-L1 and other targeted genomic biomarkers, or because the patients progressed on treatments indicated by prior testing. KEYTRUDA, for example, is indicated for the treatment of patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options. References: KEYTRUDA (pembrolizumab) package insert: https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf TECENTRIQ (atezolizumab) package insert: https://www.gene.com/download/pdf/tecentriq_prescribing.pdf YERVOY (ipilimumab) package insert: https://packageinserts.bms.com/pi/pi_yervoy.pdf | 4/21/2021 3:24 PM |
| 7 | Strike the word 'advanced' | 4/20/2021 5:32 PM |
| 8 | suggestions should be agregated about which test to use as a complement | 4/7/2021 2:20 PM |
| 9 | TMB is not as good predictor of IO-response as PD-L1 IHC or CD274 mRNA level is. Combination is best. TMB testing and reporting needs to be standardized. Currently TMB literature is just as hard to follow as PD-L1 literature is. | 4/6/2021 6:11 AM |
| 10 | It seems like this statement is off topic (i.e. not specifically dealing with PD-L1 IHC). Also, this is contrary to the June 16, 2020 FDA approval: "Food and Drug Administration granted accelerated approval to pembrolizumab (KEYTRUDA, Merck & Co., Inc.) for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB H) [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options." Although the explanation for this statement is not provided, it feels like this is more of an opinion of the panelists who might be biased against TMB being used as an additional biomarker. | 4/3/2021 4:26 PM |
| 11 | Not to use alone implies that it could be used with company. It would be useful to flesh out the statement further. | 4/1/2021 6:56 PM |
| 12 | We should ABSOLUTELY NOT be in the business of dictating to clinicians how to select therapies or select patients for specific therapies. | 4/1/2021 11:02 AM |

# Q9 How feasible is it to implement this guideline?

Answered: 77 Skipped: 53

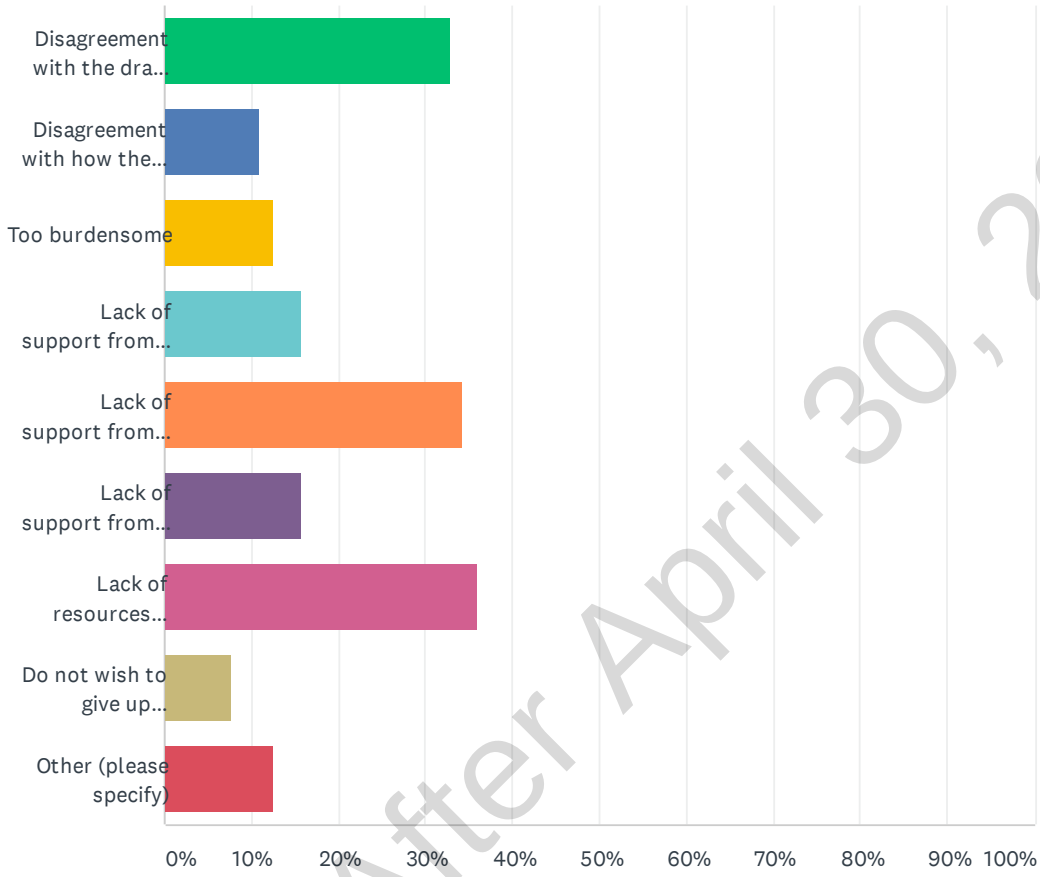



| ANSWER CHOICES | RESPONSES | |
|---|---|---|
| All of it is feasible to implement. | 68.83% | 53 |
| Parts of it are feasible to implement. | 29.87% | 23 |
| None of it is feasible to implement. | 1.30% | 1 |
| TOTAL | | 77 |

| # | COMMENTS ABOUT THE FEASIBILITY OF IMPLEMENTING THE GUIDELINE: | DATE |
|---|---|---|
| 1 | The parts of the guideline that are internal to pathology are likely feasible to implement; recommendations like use of TMB for therapeutic considerations require buy-in from oncologists. | 4/30/2021 3:21 PM |
| 2 | problem for low volume laboratories. not clear if all or some antibodies can be used interchangeably | 4/28/2021 10:03 AM |
| 3 | I am not sure this has any value, and it can get well-intentioned, good clinicians in trouble. | 4/26/2021 11:20 AM |
| 4 | Not terribly feasible to implement in smaller labs and health systems with lower volumes. | 4/22/2021 10:26 AM |
| 5 | Given that both clinicians and pathologists are instructed in the guidelines, and that practices are somewhat established, it will be slow going to change people's habits and billing/revenue streams. Worthwhile, though. (see responses to next question) | 4/21/2021 10:19 AM |
| 6 | The quality of validation is variable and could sometimes be questionable. | 4/5/2021 12:32 PM |
| 7 | Missing box for comments on validation. One cannot validate ALL specimen types and ALL fixatives. That is unreasonable. One should be able to have a comment for certain fixatives, decalcified tissue, etc...like any other marker. | 4/4/2021 2:21 PM |
| 8 | All of it seems feasible. Labs can review the guideline, and develop their documentation template to cover these issues. | 4/1/2021 1:50 PM |
| 9 | It would be helpful if this guideline indicated support for the use of PD-L1 LDT testing. | 4/1/2021 1:43 PM |
| 10 | Validation across multiple antibodies, platforms, and specimen types will be a challenge for some laboratories. | 4/1/2021 11:05 AM |
| 11 | Some scoring systems and assays are still evolving | 3/31/2021 9:09 PM |

# Q10 What barriers might impede adoption of the final guideline? (Choose all that apply.)

Answered: 64 Skipped: 66





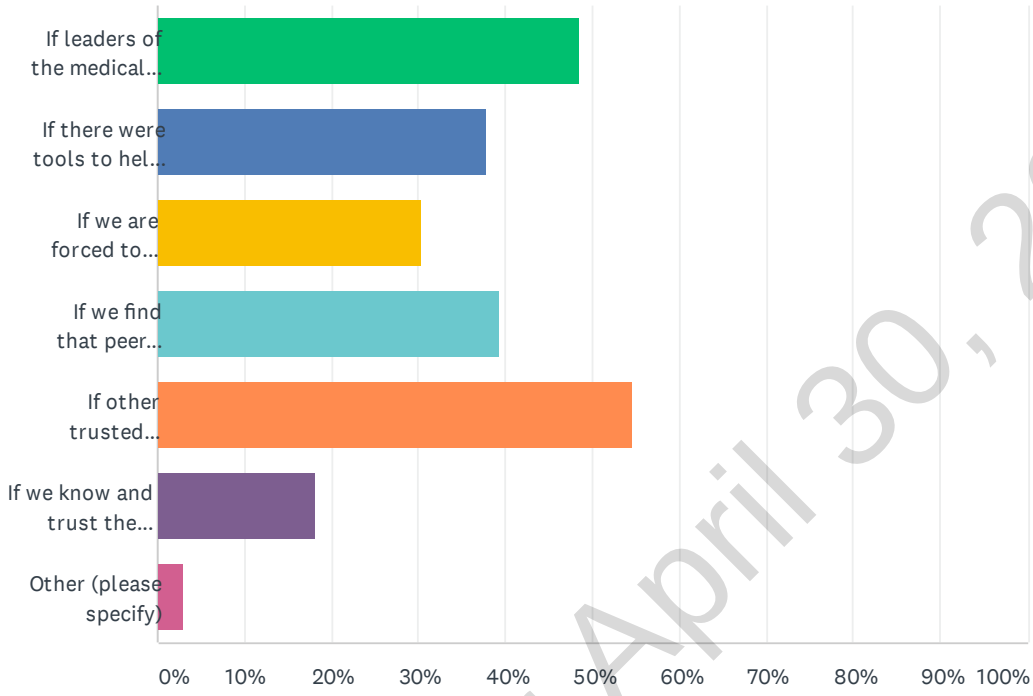

| ANSWER CHOICES | RESPONSES | |
|---|---|---|
| Disagreement with the draft recommendations | 32.81% | 21 |
| Disagreement with how the guideline was developed | 10.94% | 7 |
| Too burdensome | 12.50% | 8 |
| Lack of support from administration | 15.63% | 10 |
| Lack of support from other members of the medical team | 34.38% | 22 |
| Lack of support from the community (others outside your institution e.g., patients, industry) | 15.63% | 10 |
| Lack of resources (funding) | 35.94% | 23 |
| Do not wish to give up personal autonomy to follow the guideline | 7.81% | 5 |
| Other (please specify) | 12.50% | 8 |
| Total Respondents: 64 | | |

| # | OTHER (PLEASE SPECIFY) | DATE |
|---|---|---|

| | | |
|---|---|---|
| 1 | There should be a statement on how the guideline was developed, e.g. following systematic review? | 4/28/2021 8:52 AM |
| 2 | commercial assays do not always perform, as good as they should do according to EQA. LDT may have the same characteristic, but can do as good, and is less expensive | 4/26/2021 5:45 AM |
| 3 | In our Centre, none of the above mentioned barriers might impede the adoption of these guidelines. | 4/26/2021 3:59 AM |
| 4 | We are thankful that the committee is collecting information on potential barriers to adoption of the final guideline and seems to put emphasis that all (advanced) NSCLC patients should receive PD-L1 testing along with molecular profiling. | 4/22/2021 10:14 PM |
| 5 | Lack of evidence supporting the clinical utility of the biomarker in toto, owing to poor clinical concordance of biomarker testing results to outcomes, without comparative assessment of the different contributing assays or LDT's to the outcomes | 4/20/2021 5:50 AM |
| 6 | Reimbursement issue may interfere with optimal practice | 4/8/2021 3:35 PM |
| 7 | Important that adequate resources are given to laboratories that undertake this work | 4/4/2021 6:44 AM |
| 8 | Finding suitable validation material as not only the percentage is important, but also the staining intensity. | 3/31/2021 7:43 PM |

# Q11 What facilitators might assist in your adoption of the final guideline? (Please select your top 3 facilitators.)

Answered: 66 Skipped: 64




| ANSWER CHOICES | RESPONSES | |
|---|---|---|
| If leaders of the medical staff discussed adoption/adaption of the guideline for our practice setting | 48.48% | 32 |
| If there were tools to help implement the guideline | 37.88% | 25 |
| If we are forced to comply with the guideline by administration or an accreditation body | 30.30% | 20 |
| If we find that peer institutions/practices adopt the guideline | 39.39% | 26 |
| If other trusted organizations endorse the guideline | 54.55% | 36 |
| If we know and trust the members of the panel members and/or organizations who developed the guideline | 18.18% | 12 |
| Other (please specify) | 3.03% | 2 |
| Total Respondents: 66 | | |

| # | OTHER (PLEASE SPECIFY) | DATE |
|---|---|---|
| 1 | It may seem beneficial if current testing rates in academic centers, community practice and by geographical area could be incorporated into the guideline publication or a separate publication that helps institutions/practices to measure their compliance with the PD-L1 testing guidelines. | 4/22/2021 10:14 PM |
| 2 | If oncologists asked for implementation of the guideline | 4/20/2021 5:50 AM |

# Q12 Please provide any general comments or concerns:

Answered: 10 Skipped: 120

| # | RESPONSES | DATE |
|---|---|---|
| 1 | IS IT POSSIBLE A (?) Statement 7 Concerning defined antibody for drug prescription when not othetwise validated, the refferred antibody slhould be applied. This point relates with countries where drug prescription might be linked to defined companion biomarker, not possible to overlook, as the rule nedds to be followed. | 4/27/2021 1:11 PM |
| 2 | I fear that "Guidelines" can stifle the wise judgment of good doctors, rather than promote better care. Guideline development is not a means of developing new ideas. PDL1 testing by IHC seems to need lots of improvement: Improving the clinical value of PDL1 IHC can't be done at this time by anchoring practices in place with guidelines. I am not sure this new set of Guidelines has much value at this point in time. | 4/26/2021 11:20 AM |
| 3 | International accreditation of biomarkers such as EQA Lung or others are fundamental to assist and improve the correct PD-L1 immunostaining, both for assay and interpretation. | 4/26/2021 3:59 AM |
| 4 | The committee may consider incorporating an outlook on the future role of digitally-supported assay scoring. | 4/22/2021 10:14 PM |
| 5 | The guideline about selecting/using the optimal specimen should assign that task to the PATHOLOGIST, not the CLINICIAN. | 4/21/2021 10:19 AM |
| 6 | No Comment box for Statement box #2 : Specimen pre-analytics should be adhered to as outlined in the manufacturers package insert. It is important and for more than just patient safety that a lab validate a 'predictive' clinical biomarker as used in the clinical trials using the clinical outcome data. It is increasing apparent that LDT, esp. for PD-L1, have higher rates of false negative results than their FDA-approved assay equivalents. | 4/20/2021 5:41 PM |
| 7 | same comment: Please write "CD274 (PD-L1)". If that's not possible, please write "PD-L1 (CD274)" as a second choice. Please see an opinion paper by The Gene Product Nomenclature Consortium (GPNC), Fujiyoshi K et al. PNAS 2021 on this very issue at https://www.pnas.org/content/118/3/e2025207118 | 4/15/2021 1:07 PM |
| 8 | My key concern would be which PDL1 antibody should be used for validation. PDL1 testing is very complicated because there are different interpretations rules for each antibody and each individual tumor type and each type of FDA approved therapy. Without the clinical trial data to support the efficacy of "off label" antibody testing, how can we ensure that the results mean the same thing clinically? Also, the guidelines do not address the interpretation of the antibodies. I think this is absolutely critical that interpretation must be done by pathologists who are adequately trained and have been deemed competent. Are there standardized competency tests? The nuances of interpretation are very hard to keep track of. | 4/15/2021 9:30 AM |
| 9 | The TMB recommendation may receive criticism from the oncology community, since they seem to be frequently requesting this be performed to guide treatment decisions. | 4/8/2021 11:14 PM |
| 10 | Well done. | 3/31/2021 2:22 PM |